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**Health and Environmental Effects
Profile for 1, 3-Butadiene**

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR 1,3-BUTADIENE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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EXECUTIVE SUMMARY

1,3-Butadiene is a colorless gas at room temperature and is mildly aromatic. The major uses of butadiene are in the manufacture of rubber, plastics, resins and fabrics. In the atmosphere, butadiene may react photochemically. Perhaps the most important fate determining process of atmospheric butadiene is its reaction with hydroxyl radicals. The half-life of this interaction has been estimated to be 0.25 hour. Small amounts of butadiene present in surface waters may undergo vaporization, biodegradation and chemical reaction. The relative importance of these processes has not been evaluated with certainty.

Because of lack of monitoring data, it is not possible to estimate the human intake of butadiene from water, foods and skin exposure. The human inhalation intake of butadiene is estimated to be 0.045 mg/day.

Early reports of the toxic effects of butadiene vapor in humans show that exposure may result in lethargy, drowsiness and irritation to the eyes and mucous membranes. Long-term effects in humans of butadiene exposure have not been reported in the literature. Animal studies reveal that butadiene is of relatively low toxicity. For rats and mice, the LC_{50} is $>250,000 \text{ mg/m}^3$. Butadiene has been reported to be mutagenic in the Ames Salmonella assay system. Results from a study conducted by Hazelton Laboratories suggest an association between inhalation exposure to butadiene and tumor formation in rats (Owen, 1981). The animal evidence would be classified by IARC (International Agency for Research against Cancer) criteria as limited.

The only information found regarding the aquatic toxicity of 1,3-butadiene was an acute lethal dose level; the 24-hour LC_{50} for the pin perch, Lagodon rhomboides (marine species), was 71.5 ppm.

1. INTRODUCTION

1,3-Butadiene (biethylene, α -butadiene, divinyl, erythrene, 1-methylallene, vinyl ethylene) is a colorless gas at room temperature and is mildly aromatic. In the United States, three main routes are used commercially to obtain butadiene. Two are dehydrogenation processes via either n-butane or n-butene. The third route is as a co-product of ethylene manufacture. Miller (1978) reports a trend to phase out dehydrogenation in favor of co-production by cracking naphtha and light oil. Some physical parameters are:

CAS registry number	106-99-0
Formula	C_4H_6
Molecular weight	54.09
Melting point	-108.915°C (Clayton and Clayton, 1981)
Boiling point	-4.413°C (Clayton and Clayton, 1981)
Density	0.6211 g/ml at 20°C (Clayton and Clayton, 1981)
Flash point	-76.1°C (Clayton and Clayton, 1981)
Vapor pressure	1840 mm at 20°C (Clayton and Clayton, 1981)
Solubility in water	733 mg/l at 25°C (McAulliffe, 1966)
Log octanol-water partition coefficient	1.99 (Hansch and Leo, 1981)

The United States production capacity of 1,3-butadiene in 1981 was 4.5 billion pounds. The actual production in 1981 was 3.0 billion pounds. While the production capacity rose slightly to 4.6 billion pounds in 1982, the actual production in 1982 was 2.0 billion pounds. Production capacity in 1983 is projected to stay close to 1981 level, and the actual production is projected to increase slightly from 1982 to 2.4 billion pounds. The major uses of butadiene include styrene butadiene rubber (40%), polybutadiene rubber (20%), other rubber products (neoprene and nitrile) (10%), hexamethylenediamine (10%) and other miscellaneous products including resins (20%) (C&EN, 1982; Miller, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

In the atmosphere, butadiene may participate in photolysis reactions. Stephens and Burleson (1967) collected ambient air samples from Riverside, California, containing 2-9 ppb butadiene and subjected the samples to UV light (blacklite bulbs). After 1 hour, the amount of butadiene was less than half the original concentration, and no butadiene was detected after 4 hours.

The reactivity of atmospheric butadiene with NO_x , O_3 and radicals such as OH , $\text{O}(^3\text{P})$, and OH has been studied by a number of authors. The reactivity of butadiene (2 ppm) in the presence of 1 ppm NO_x and 55% relative humidity was studied by Yanagihara et al. (1977) in a smog chamber at 30°C . When the mixture was irradiated with light at wavelengths of 345-355 nm and an intensity of $700 \mu\text{W}/\text{cm}^2$, 100% of the butadiene disappeared in 5 hours. Similarly, Kopczynski et al. (1972) observed a 100% decrease of butadiene concentration when a mixture of hydrocarbons containing butadiene (total hydrocarbon concentration of 4529 ppb C) and NO_x (870 ppb) was irradiated with sunlight for 6 hours at 23.9 - 30.6°C . Altshuller et al. (1970) observed a 50% degradation of butadiene when Los Angeles air (morning peak traffic) was irradiated in Tedlar bags with sunlight for 2 hours. The products of butadiene and NO_x photooxidation were acrolein, aliphatic aldehydes, formaldehyde, ethylene, ozone and peroxyacetyl nitrate (Altshuller et al., 1966; Huess and Glasson, 1968). Glasson and Tuesday (1970) concluded that thermal oxidation of butadiene would be relatively unimportant in polluted atmospheres when compared with photooxidation.

The rate constant for O_3 reaction with butadiene was determined to be $8.4 \times 10^{-18} \text{ cm}^3/\text{molecule-sec}$ by Japar et al. (1974) and $6.6 \times 10^{-18} \text{ cm}^3$

per molecule-sec by Hampson (1980). The rate constants for gas phase butadiene reaction with O(3p) and OH at 25°C were determined to be 1.9×10^{-11} cm³/molecule-sec and 6.9×10^{-11} cm³/molecule-sec, respectively (Gaffney and Levine, 1979). Darnall et al. (1976) estimated the rate constant for an OH• radical reaction with butadiene at 27°C to be 7.6×10^{-11} cm³/molecule-sec. Assuming the typical average atmospheric concentrations for OH•, O(3p) and O₃ to be 10⁷ molecules/cm³ (Darnall et al., 1976), 2.5×10^4 molecules/cm³ and 1.0×10^{12} molecules/cm³ (Graedel, 1978), respectively, it can be concluded that OH• radical reactions with butadiene would be the fate determining process in the atmosphere. Darnall et al. (1976) calculated the half-life for an OH• radical reaction with butadiene at 27°C has been calculated to be 0.25 hour. The presence of 0.1 ppm of O₃ in the atmosphere changed the half-life to 0.24 hour (Darnall et al., 1976).

2.2. WATER

Butadiene is not likely to be released in large quantities to the environment (Miller, 1978). If large amounts of butadiene contact a water body, as might occur in a transportation accident, it will float and boil on the water forming a flammable visible vapor cloud (Miller, 1978). Smaller amounts of butadiene in water may undergo vaporization, biodegradation and chemical reactions in the water. The half-life for evaporation of butadiene from water has been calculated using the method of Mackay and Leinonen (1975) to be about 4 hours from 1 meter depth of water. In situations where the water body is turbulent, for example, in a fast-flowing river, the liquid phase mass transfer coefficient may be considerably higher and the evaporation rate will increase correspondingly (Mackay and Leinonen, 1975). Therefore, evaporation may be the most important removal process of butadiene from aquatic media.

A number of investigators have shown that 1,3-butadiene can be degraded by species of microorganisms isolated from soil and surface water. For example, Mycobacterium E20 (DeBont et al., 1979), Nocardia sp. 249 (Watkinson and Somerville, 1976), Methylosinus sp. (CRL-15), (Patel et al., 1979), and Methylosinus trichosporium 08 36 (Hou et al., 1979) have been shown to biodegrade butadiene. However, little information is available regarding the biodegradability of butadiene in natural waters or soils where a mixture of microorganisms may be present. The biodegradation rate constant for 1,3-butadiene in aquatic media has been estimated to be 3×10^{-9} ml cell⁻¹ hour⁻¹ (Burns et al., 1981); the half-life for biodegradation of 1,3-butadiene can be estimated to be ~19 days. Therefore, biodegradation of this compound in natural aquatic environment may not be significant when compared with other processes.

The chemical reactivity of 1,3-butadiene in natural aquatic media because of its hydrolysis and photolysis are not significant fate determining processes (Mabey et al., 1982). Based on the estimated rate constant ($2 \text{ M}^{-1} \text{ sec}^{-1}$) (Mabey et al., 1982) and the estimated concentration of peroxy radicals (10^{-9} M) in aquatic media (Mill and Mabey, 1980), the oxidation of 1,3-butadiene in aquatic systems by peroxy radicals can be considered to be an insignificant process. However, the half-life for the reaction of singlet oxygen ($^1\text{O}_2$) with 1,3-butadiene in aquatic media can be calculated to be <1 day from the estimated rate constant of $1 \times 10^7 \text{ sec}^{-1}$ (Mabey et al., 1982) and the concentration of $^1\text{O}_2$ in aquatic media of 10^{-12} M (Mill and Mabey, 1980). Therefore, this oxidation may play a significant role in determining the fate of residual 1,3-butadiene in aquatic media.

2.3. SOIL

Virtually no experimental data on the fate and transport of 1,3-butadiene in soil is available. Assuming the correlation equation of Schwarzenbach and Westall (1981), a value of 1.99 for the logarithm of octanol/water partition coefficient and a value of 0.1% organic carbon content of soil, the sorption partition coefficient for this compound in soil is calculated to be 0.08. Therefore, this compound is expected to be weakly sorbed onto soil. In a situation where the monomer might be released, for example from storage tanks or in transportation accidents, butadiene is likely to vaporize from soil and enter the atmosphere. The residual butadiene may be transported by rainwater to different land area, surface water or to groundwater. The amount of butadiene reaching a different land area or water body will depend on the microbial and chemical oxidation fate processes of the compound in soil. Unless more experimental or theoretical data become available, it is difficult to predict these fate processes in soil.

2.4. SUMMARY

The fate of a chemical predicted from theoretical calculations, in certain instances, may vary considerably from the experimental data. In the preceding discussions, the fate of 1,3-butadiene due to likely environment processes has been predicted from theoretical equations only when experimental data were not available. However, extreme caution should be exercised in interpreting the predicted fate data based on theoretical calculations alone.

3. EXPOSURE

3.1. WATER

Although butadiene may be present in wastewater from butadiene manufacture (Miller, 1978) and in river water (Ewing et al., 1977), no report of its presence in drinking water could be found.

3.2. FOOD

Pertinent data regarding the level of butadiene in food were not located in the available literature.

3.3. AIR

A few investigators detected, and in some cases quantified, the amount of a mixture of butadiene and 2-butene present in ambient air (Louw et al., 1977; Siddiqui and Worley, 1977; Miller and Alkezweeny, 1980; Sella, 1979). The analytical method used by these investigators could not separate 1,3-butadiene from 2-butene. The ambient air levels of 1,3-butadiene measured by various investigators are shown in Table 3-1. A recent report (Brodzinsky and Singh, 1982) summarized the ambient air concentrations of 1,3-butadiene from both urban/suburban and source areas in the United States. The mean ambient air concentrations of 1,3-butadiene in urban/suburban and source areas have been reported to be 1.7 and 4.2 ppb, respectively.

It can be concluded from the report of Brodzinsky and Singh (1982) that the concentration of 1,3-butadiene in ambient air near urban/suburban areas should be about 2 ppb ($\sim 4.5 \times 10^{-3}$ mg/m³). Assuming that an individual inhales 20 m³ of air/day and retains half of the contaminant (0.5), the daily intake of 1,3-butadiene through inhalation should amount to 0.045 mg.

3.4. DERMAL

Pertinent data regarding the effects of dermal exposure to 1,3-butadiene were not located in the available literature.

TABLE 3-1
Ambient Air Levels of 1,3-Butadiene

Locality	Concentration (ppb)	Reference
Los Angeles, CA	2.0 ^a	Altshuller et al., 1971
Azusa, CA	1.0 ^a	Altshuller et al., 1971
Riverside, CA	2.6-9.0	Stephens and Burleson, 1967
Los Angeles, CA	ND - 9.0	Neligan, 1962
Houston area, TX	ND - 33.3 ^b	Lonneman et al., 1979

^aAverage value

^bSampling locations include industrial areas and tunnels

ND = Not detected

4. PHARMACOKINETICS

4.1. ABSORPTION

Carpenter et al. (1944) reported that the distribution coefficient for butadiene between blood and air was 0.603 in vitro and 0.645 in vivo, indicating that the passage of butadiene from inspired air into the blood is a process of simple diffusion of the gas from the alveoli. Other information was not found.

4.2. DISTRIBUTION

Shugaev (1969), a Russian investigator, measured the distribution of butadiene in several tissues in rats following inhalation exposure. The animals were exposed to 285,000 mg/m³ for 2 hours. There was a high concentration of butadiene in the perinephric fat (152 mg percent) with lower levels in the brain (51 mg percent), liver (51.4 mg percent), septum (45 mg percent) and kidney (36 mg percent). The time interval following inhalation exposure and tissue level determination was not stated. Rats were also exposed to 285,000 mg/m³ of butadiene for 1 hour. Tissue levels of butadiene determined 0.1 minute following exposure showed that levels were about 35 mg percent in the brain and 34 mg percent in the liver. These levels decreased with time, and at 90 minutes following inhalation exposure only trace levels of butadiene could be determined in the two tissues. Shugaev (1969) also determined the distribution of butadiene in the central nervous system and liver in two cats exposed to levels of butadiene that were unspecified but high enough to cause death within 1 hour. High concentrations of butadiene were found in the spinal cord and pores.

Carpenter et al. (1944) exposed rabbits to 250,000 ppm butadiene. After 9 minutes, the butadiene concentration was 0.26 mg/ml in the femoral artery and 0.18 mg/ml in the femoral vein.

4.3. METABOLISM

Herschleb and Leibman (1972) reported in an abstract that when 1,3-butadiene was incubated with rat liver supernatant fractions and NADPH-generating systems, extracts of the reaction mixture contained 3-butene-1,2-diol and 1,2,3,4-tetrahydroxybutane.

Bedford (1975) postulated that an intermediate 1,2-epoxybutene-3 was formed before the generation of the metabolites reported by Herschleb and Leibman (1972). The existence of this intermediate was later confirmed by Malvoisin et al. (1979), who incubated 1,3-butadiene in the presence of rat liver microsomes supplemented with a NADPH-generating system and found the compound 1,2-epoxybutene-3 to be one of the major metabolites.

DeMeester et al. (1978) have suggested that butadiene monoxide might be a possible primary metabolite of butadiene. An earlier report stated that rabbits exposed to 6700 ppm butadiene for 7.5 hours/day, 6 days/week for 8 months and to 200,000-250,000 ppm butadiene for short periods of time (exact exposure schedule not specified) did not exhibit any metabolic products of butadiene in the urine (Carpenter et al., 1944).

4.4. EXCRETION

Pertinent data regarding the excretion of butadiene were not located in the available literature.

5. EFFECTS

5.1. CARCINOGENICITY

Hazelton Laboratories (Owen, 1981) performed a study of the carcinogenicity of 1,3-butadiene to rats. Groups of 110 male and 110 female Sprague-Dawley rats were exposed to 0, 1000 or 8000 ppm (0, 2212 or 17,701 mg/m^3) of 1,3-butadiene by inhalation for 6 hours/day, 5 days/week for 105 weeks (females) and 111 weeks (males). During months 2 through 5 of exposure, the high exposure animals had clinical signs of toxicity (slight ataxia and excess secretion from the eyes and nose). A statistically significant, dose-related decrease in survival was observed in treated groups. Butadiene exposure did not affect hematologic, blood chemical and urinalysis parameters, or performance in a neuromuscular test, but was associated with increased liver weights. No structural changes were detected in livers of treated animals as compared with those of controls. Examination of the 10 animals/sex/group killed after 52 weeks of exposure did not disclose any evidence of systemic toxicity or carcinogenicity.

However, statistically significantly increased incidences of both common and uncommon tumor types were associated with exposure to 1000 and 8000 ppm butadiene for the duration of the experiment. Increased incidences of mammary tumors, thyroid follicular tumors and uterine/vaginal stromal tumors were observed in females, while increased incidences of Leydig cell tumors and pancreatic exocrine tumors were found in males. Both sexes had an increase in the incidence of Zymbal gland tumors.

It has been suggested that two possible oxidation metabolites of butadiene, butadiene monoxide and more especially diepoxybutane, have carcinogenic properties (Van Duuren et al., 1963, 1965, 1966).

Van Duuren et al. (1963) conducted skin-painting experiments with 1,2-epoxybutene-3. Thirty male Swiss-Millerton mice were skin-painted 3 times/week with a brush that delivered ~100 mg of the compound to the backs of the animals. The animals were ~8 weeks old at the beginning of treatment and the median survival time was 237 days. Three tumors developed in the animals, one of which was malignant. In the control groups that received no treatment, 5% of the 267 animals developed tumors, 1 of which was a squamous cell carcinoma. The review of this study by the International Agency for Research on Cancer (IARC, 1976) concluded that the data does not allow an evaluation of carcinogenic risk. However, a reevaluation of the more recent animal evidence for the carcinogenicity of this compound by the Carcinogen Assessment Group (CAG) of EPA using IARC criteria suggests a classification of limited.

5.2. MUTAGENICITY

DeMeester et al. (1980a) reported that gaseous butadiene (atmosphere containing 16% butadiene) was mutagenic toward S. typhimurium strain TA1530 in the presence of a NADPH-fortified rat liver microsomal preparation (prepared from rats pretreated with either Aroclor 1254 or phenobarbitone). A significant mutagenic effect was also observed when petri dishes containing the S. typhimurium strain, but no metabolic activation system, was incubated in the presence of butadiene with other plates in which the S-9 rat liver fraction had been added. The authors attribute this indirect mutagenic effect to the formation, by the S-9 mix, of volatile intermediates that migrated and induced mutation in neighboring bacteria. This is in concordance with the data reported by Poncelet et al. (1980), who used the same concentration of butadiene and the same strain of S. typhimurium and found that the mutagenicity was relative to the S-9 concentration in the mix.

These data vary from those of earlier published reports by DeMeester et al. (1978, 1979, 1980b) in which a direct mutagenic effect (no liver activation system) of butadiene was reported with S. typhimurium. DeMeester et al. (1980a) attribute these previous positive interpretations to experimental artifacts.

5.3. TERATOGENICITY

1,3-Butadiene has been tested for teratogenicity by Hazleton Laboratories (Irvine, 1981). Groups of 24 pregnant female Sprague-Dawley CD rats were exposed by inhalation to 200, 1000 or 8000 ppm butadiene for 6 hours/day on days 6 through 15 of gestation. A group of 40 similar pregnant rats served as sham-exposed controls. Dams in the highest exposure group had an initial weight loss and their fetuses had statistically significantly lower mean weights and crown-rump lengths than did control fetuses. The incidence of minor skeletal defects and variants was higher in the butadiene-exposed groups than in controls. This finding was associated with reduced fetal size in the exposed groups.

Soviet investigators, Serebrennikov and Ogleznev (1978), reported in an abstract that inhalation of maximum permissible concentrations of butadiene (exact concentration and dosing schedule not specified) by female rats for 4 months resulted in an increased frequency of teratogenesis (parameter measured, unspecified) from 3.0-22.5%, and increased embryonal mortality from 7.5-44.0%.

In summary, much higher doses than those encountered in the environment over extended periods appear to be required for fetotoxicity, and in that case (Irvine, 1981) maternal toxicity was present.

5.4. OTHER REPRODUCTIVE EFFECTS

Carpenter et al. (1944) exposed groups of laboratory animals to butadiene-air mixtures of 0, 600, 2300 and 6700 ppm for 8 months. For rats, the average number of litters/female was decreased, especially in 2300 and 6700 ppm groups. The number of litters/female were 3.3, 2.72, 2.5 and 2.62 for the 0, 600, 2300 and 6700 ppm groups, respectively. However, the average number of young in a litter was increased in all the groups as compared with the norm of 6 young/litter. The average number of pups/litter was 7.8, 8.4, 7.9 and 7.8, respectively, for the 0, 600, 2300 and 6700 ppm groups. The data obtained from guinea pigs and rabbits supported the contention that fertility was not impaired by inhalation exposure to butadiene. All guinea pig exposed groups were about equivalent in the number of progeny when compared with controls. While the rabbits in the 600 or 2300 ppm groups had no litters, the control and 6700 ppm groups had 24 and 27 pups, respectively. Histologic examination of the testes did not show any evidence of degeneration. It was not specified if the sections were taken from the adult animals or from the embryos.

5.5. CHRONIC TOXICITY

The Hazelton Laboratories study of the carcinogenicity and toxicity of 1,3-butadiene (Owen, 1981) revealed little evidence of systemic toxicity other than slight ataxia, excess secretion from the eyes and nose, and a statistically significant dose-related decrease in survival in rats exposed chronically to 1000 or 8000 ppm of this chemical by inhalation for 6 hours/day, 5 days/week. This study is described in greater detail in Section 5.1.

Carpenter et al. (1944) exposed groups of 24 rats, 12 guinea pigs, 4 rabbits and 1 dog to butadiene-air mixtures of 0, 600, 2300 and 6700 ppm for 7.5 hours/day, 6 days/week for 8 months. Among the exposed animals, no

deaths could be attributed to the effects of butadiene. Blood parameters including hemoglobin determinations, erythrocyte, leukocyte and differential counts were not remarkable for the exposed animals. Clotting time, reticulocyte count and mean corpuscular volume were determined for the dogs and rats. There were no significant differences in these parameters between the experimental and control groups. Blood chemistry studies revealed no abnormal values for urea nitrogen, bilirubin or glucose for the exposed animals. The results of routine urinalysis for the experimental groups were unremarkable. Ophthalmoscopic examination of the eyes of the exposed dogs and rabbits disclosed no signs of injury. This finding was confirmed by histological examination of the cornea, sclera, ciliary body, retina and optic nerve, all of which were undamaged. No pathological changes were noted in the adrenals, heart, kidneys, skeletal muscles, pancreas, septa, testes or ovaries of either the exposed animals or the controls. Histological examination of the liver revealed light cloudy swelling in 68% of the exposed animals in the 6700 ppm group, while only 10% of the control group exhibited this condition.

In a related experiment, Carpenter et al. (1944) assessed the effect of butadiene on the 29 rabbits undergoing anesthesia with 25% by volume (250,000 ppm) mixture of butadiene with oxygen. They found that the average time for loss of pupillary reflex to strong light was 3.8 minutes and that death occurred at 23 minutes. Six rabbits were then exposed to either 15 or 21 consecutive daily inductions into the fourth stage of anesthesia by 200,000-250,000 ppm butadiene. Less than 2 minutes were required for loss of motor and labyrinth reflexes. The weight gain and general condition of the rabbits were not affected by the daily inductions. The authors concluded that repeated anesthesia with butadiene had no deleterious effect on either the general condition or the internal organs of rabbits.

The apparent lack of significant toxic effects of butadiene at concentrations <8000 ppm following inhalation exposure has also been demonstrated by Crouch et al. (1979), who exposed 5 groups of 40 male and 40 female Sprague-Dawley rats to 1,3-butadiene gas at atmospheric concentrations of 0, 1000, 2000, 4000 and 8000 ppm, respectively, 6 hours/day, 5 days/week for 13 weeks. Because a table of experimental data was not presented in the body of the paper, the raw data could not be assessed. What follows are the authors' own interpretations of their data.

With the exception of increased salivation reported in the female rats exposed to the higher concentrations of butadiene, particularly during the last 6-8 weeks of exposure, no other treatment-related abnormalities were observed. No effects considered attributable to exposure were observed in regard to growth rate, food consumption, hematological and blood biochemical investigation, urine analysis, erythrocyte and brain cholinesterase, erythrocyte osmotic fragility, or neutrophil phagocytosis. There was no treatment-related effect on neuro-muscular function as determined by using a modified rotating rod test. Macroscopic and histological examination of various organs showed no untoward changes related to exposure to butadiene gas.

Ripp (1967), Molodyuk (1969) and Nikiforova et al. (1969) have investigated the effects of inhalation exposure to low levels of butadiene. These studies appeared in a report by Miller (1978). The following descriptions of these studies are from Miller (1978). Apparently, all three Russian groups were reporting on the same group of animals.

Ripp (1967) exposed groups of 14-15 male albino rats to butadiene concentrations of 0, 1.07 ± 0.006 , 3.08 ± 0.006 or 30.8 ± 0.075 mg/m³ 24 hours/day for 81 days. Rats exposed to low levels of butadiene (1 or 3 mg/m³)

behaved within normal limits, while those exposed to the highest concentration displayed a certain unrest during the first days of the experiment, but gradually, toward the end of treatment, their restlessness was less pronounced. Rats exposed to 1 and 3 mg/m³ butadiene gained weight normally, but those in the 30 mg/m³ group had a normal weight gain until about day 50; after this time, weight decreased until the end of the experiment.

For all groups, values for erythrocytes, reticulocytes, hemoglobin and leukocytes were within normal limits except for a statistically significant increase in the leukocyte count on day 80 in rats exposed to 30 mg/m³. According to Ripp (1967), rats in the highest treatment group had increased cholinesterase activity [time (in minutes) for acetylcholine to be hydrolyzed], which increased throughout the experiment but then returned to the levels of the other groups after cessation of treatment. The absorption index of the serum, used to determine serum protein level, increased in rats exposed to 30 mg/m³ but not in rats exposed to lower levels of butadiene.

Arterial pressure was stable for ~2 months for all groups of rats. Rats exposed to 30 mg/m³ butadiene showed a decline in arterial pressure on the 72nd day of exposure and remained at this lower level until the end of treatment and during the recovery period. The motor activity of the rats was monitored during 3-hour periods several times/week in special chambers to electronically score movement. This parameter was unchanged in rats exposed to butadiene at 1 and 3 mg/m³ for 81 days. After 7 weeks, however, activity decreased to 60% of the pre-exposure level in rats exposed to 30 mg/m³ butadiene.

Following 81 days of exposure to butadiene, tissue sections of liver, kidney, heart, septum, brain and bone marrow were examined. At all exposure levels, the rats showed some change in the lung. At the lowest exposure

level (1 mg/m^3), there were differences in comparison with the control; however, no other details were given. There was moderately pronounced interstitial pneumonia as well as small foci of atelectasis, and emphysema in the 3 mg/m^3 group. In the 30 mg/m^3 group, there was highly developed lymphoid tissue, small foci of atelectasis and emphysema.

Nikiforova et al. (1969) reported that there were no hepatic alterations in the animals subjected to 1 or 3 mg/m^3 butadiene. In the 30 mg/m^3 , there was a thinning of the trabeculae and, in some animals, almost total absence of light cells.

Molodyuk (1969) reported that the spleen showed an excess of erythrocytes in those rats exposed to 1 mg/m^3 butadiene. At 3 mg/m^3 there were indistinct nuclei of the connective tissue, plethora of vessels, and a reduction of RNA. More pronounced changes occurred in rats exposed to 30 mg/m^3 . The endothelium was swollen; vessels and sinuses revealed small hemorrhages and were plethoric. Throughout the follicles there were reticular cells, lymphoblasts and macrophages. Also, the capsule and trabeculae were loosened and there was enlargement of the lymphoid follicles.

Ripp (1967) further reported that no microscopic changes in the kidneys were seen in rats exposed to 1 mg/m^3 ; however, at 3 mg/m^3 , the changes observed were: loosening of the capsule, accumulation of connective tissue cells, excessive hyperemia of the glomerular capillaries; and in a few instances, deformation of the epithelial cell nuclei in the convoluted tubule. More pronounced changes were seen at the 30 mg/m^3 level and included: loosening of the adipose capsule and hyperemia, swelling of the glomeruli, capsules, tubular lumen and convoluted tubular epithelia; focal proliferation of connective tissue elements, macrophages and plasma cells; and reduction in the RNA level of some tissues.

Finally, Nikiforova et al. (1969) stated that the heart showed some vessels to be hyperemic and infiltrated by leukocytes in the group exposed to 1 mg/m^3 . The heart of the animals exposed to 3 mg/m^3 exhibited reduced differentiation of the endothelium, deformation of endothelial nuclei, and capillary hyperemia and hemostasis. In the highest exposure group, there was cardiac hyperemia; hemostasis hemorrhage and the RNA level of the cell cytoplasm was reduced.

In another Russian study also discussed by Miller (1978), Batkina (1966) exposed albino rats and rabbits (sex, species and number unspecified) to butadiene at concentrations of 10, 100 and 2200 mg/m^3 4 hours/day for 4 months. Reaction time to a conditioned sound was prolonged following exposure to butadiene. The reaction time was 0.33 seconds in controls, 1.04 seconds in the 100 mg/m^3 group and 0.74 seconds in the 2200 mg/m^3 group. No data regarding the 10 mg/m^3 were presented. Hematological changes included reduced leukocyte counts (40% lower in rats given 2200 mg/m^3) and alterations in serum protein concentrations. In rabbits, there was an inhibition in serum cholinesterase at the two higher dose levels and a decrease in the phagocytic activity of neutrophils.

Donetskaya and Shvartsapel (1970), again summarized by Miller (1978) administered daily oral doses of 100 mg/kg butadiene in vegetable oil to 25 rats for 2.5 months, while 10 control rats received vegetable oil. Microscopic sections revealed degenerative, sometimes necrotic, changes in the cytoplasm of cells of the heart, liver, kidneys, nervous tissue and vascular walls. The authors suggest that these microscopic changes are related to butadiene to a certain degree; it was not stated clearly whether the changes occurred in the control animals. Venous hyperemia, stasis, hemorrhage and edema were more pronounced in the experimental animals than in the controls.

Shvartsapel (1970), also cited in Miller (1978), administered butadiene to 36 rabbits by gavage for 7 months. The doses were 0.0, 0.4, 4.0 and 40.0 mg/kg/bw of butadiene in vegetable oil (dose schedule unspecified). No changes in whole blood free sulfhydryl (SH) concentration, serum acetylcholinesterase or cholinesterase levels were observed, and no raw data were presented. In the highest dose group, there was a significant increase in the activity of enzyme fructosediphosphate aldolase during the seventh month, and a slight decrease in hemoglobin after the fourth month. Animals at the lower concentration levels did not suffer from these effects.

Several studies reported in abstracts by Russian investigators deal with occupational exposure to butadiene and other chemicals in the rubber industry. The range of findings include systemic manifestations, headache, weakness, sweating; alterations in enzyme levels; abnormal hepatobiliary functions, as well as other disturbances (Putalova, 1979; Mukhametova et al., 1976; Sergeta et al., 1977; Sergeta et al., 1975). Unfortunately, many of the details of these studies are not known and, therefore, the studies are of limited usefulness.

5.6. ACUTE TOXICITY

5.6.1. Human. Von Oettingen (1940) reported that inhalation of a 1% (22,130 mg/m³) mixture of butadiene in air for 5 minutes had no effect on respiration or blood pressure; however, a slight quickening of the pulse, a slight feeling of dryness and prickling in the mouth and nose were noted. Twenty 2-hour exposures to 140,000 mg/m³ caused some irritation to the lungs, spleen and slight hyperplasia of the bone marrow. Further details concerning the study were not available.

Miller (1978) reviewed the work of MCA (1974) and Steere (1968) and reported that exposure to butadiene at concentrations $<44,260 \text{ mg/m}^3$ resulted in a mild narcotic effect. Unfortunately, a lower limit of exposure was not stated and it seems unlikely that at negligible concentrations butadiene would cause a mild narcotic effect. Minor irritation to the eyes and mucous membranes of the upper respiratory tract and asphyxiation have resulted from exposure to butadiene (MCA, 1974; Steere, 1968).

Carpenter et al. (1944) investigated the psychomotor responses of two human volunteers exposed to concentrations of 2000, 4000 and 8000 ppm butadiene for 7, 6 and 8 hours, respectively. Tapping rate and steadiness tests were used to assess the psychomotor functioning. The subjective symptoms reported at the two lower dose levels were slight smarting of the eyes and difficulty in focusing on instrument scales. At the 8000 ppm concentration, no subjective symptoms were reported. The authors suggested that this was attributable to slight anxiety over the possibility of an explosion from local high concentration at the butadiene cylinder. The results on the tapping test as a means of evaluating psychomotor response were inconclusive, and the results of the steadiness test showed that at a concentration of 8000 ppm butadiene, the subjects performed better than at the 4000 ppm level. The authors conclude that the subjects were probably physically or mentally below par on the day of the 4000 ppm test and, therefore, performed poorly.

Wilson (1944) reported that workers exposed to butadiene vapor in the manufacture of rubber complained of irritation of the eyes, nasal passages, throat and lungs. Coughing, fatigue and drowsiness were symptoms in some of the workers. All symptoms disappeared after the workers were no longer exposed to the vapors. The concentration of the chemical was described only

as "not heavy." Subsequent exposures resulted in reoccurrence of the symptoms. Physical examinations were performed and unspecified blood chemistry and urinalysis results were negative.

According to Altschuller et al. (1966), eye irritation following exposure to the photooxidation products of butadiene and nitrogen oxide mixtures was determined on a severity scale of 0-30 by a group of 10 or 15 panelists who found that the higher the score, the more severe the eye irritation; the butadiene-nitrogen oxide products scored 20. No information concerning the qualifications of the panelists or the criteria for evaluating the eye irritation were available. In addition, a mixture of butadiene and nitrogen oxide was used; hence, there is no certainty that the effects were due primarily to the butadiene.

Ripp (1967) investigated the effect of butadiene on the eyes. Four subjects (ages 20-35 years) breathed from a cylinder containing pure air and then from a cylinder into which butadiene was introduced at a concentration of 3.6-4.2 mg/m³. At the lowest concentration, there was no change in irritation in any subjects, while at the higher concentrations there was a significant increase in irritation in all the subjects. The parameters for measuring irritation were not described.

Superficial burns can develop from absorption of butadiene through the skin or clothing. Dermal contact with liquid butadiene results in a sensation of cold followed by a burning sensation (MCA, 1974; Lefaux, 1968).

5.6.2. Animals. Experiments with laboratory animals have shown that the toxicity of butadiene is low. The oral LD₅₀ was 5480 mg/kg in the rat and 3210 mg/kg in the mouse. In the rabbit, a concentration of 250,000 ppm (552,500 mg/m³) caused death within 23 minutes (Carpenter et al., 1944). Other lethal concentrations are listed in Table 5-1.

TABLE 5-1

Acute Lethal Concentration (LC) Values for 1,3-Butadiene^a

	LC (mg/m ³)	Duration	Reference
Rats ^b	LC ₁₆ = 175,000	2 hours	Shugaev, 1969
	LC ₅₀ = 285,000 (219,000-370,000) ^c	2 hours	Shugaev, 1969
	LC ₈₄ = 460,000	2 hours	Shugaev, 1969
Mice ^d	LC ₁₆ = 203,000	4 hours	Shugaev, 1969
	LC ₅₀ = 270,000 (251,000-290,000) ^c	4 hours	Shugaev, 1969
	LC ₅₀ = 259,000	NR	Batkina, 1966
	LC ₈₄ = 375,000	4 hours	Shugaev, 1969
	LC ₁₀₀ = 300,000	NR	Batkina, 1966

^aSource: Miller, 1978^bSex, strain and number tested not given.^c95% confidence limits^dSex and number tested not given by either author; albino mice used by Batkina, 1966.

NR = Not reported

Killian (1930) exposed white mice (sex and number unspecified) to concentrations of butadiene ranging from 10-40% in oxygen. A concentration of 10% caused no symptoms; however, at concentrations of 20 and 40%, narcosis developed after 6-10 and 0.67-1.0 minutes, respectively.

Von Oettingen (1940) reported that 200,000-300,000 mg/m³ of butadiene was the lowest concentration range that produced narcosis and coma in mice. Other findings associated with that concentration were irritation of the mucous membranes resulting in conjunctivitis, and nasal and bronchial inflammation.

Exposure to a 25% mixture of butadiene and oxygen caused a loss of labyrinth and motor reflexes; however, recovery after exposure was rapid (Von Oettingen, 1940).

In a Russian abstract, Zlobina and Dueva (1974) reported that butadiene at 10-50 mg/m³ exhibited allergic action when inhaled by guinea pigs.

5.7. OTHER RELEVANT INFORMATION

The rubber industry is the largest employer of butadiene monomer (Miller, 1978). A number of epidemiologic studies have suggested excess morbidity and mortality in rubber workers (McMichael et al., 1976; Fine and Peters, 1976a,b). There have also been reports of excessive mortality related to certain types of cardiovascular disease, and malignant neoplasms (including bladder, stomach, large bowel, lymphatic and hematopoietic tissues and possibly the central nervous and respiratory systems) (McMichael et al., 1976; Case and Hosker, 1954; Fox et al., 1974). However, neither butadiene nor its metabolites have been implicated as the causative agent in any of the studies (Miller, 1978). Smith and Ellis (1977) have identified 10 leukemia cases among styrene-butadiene rubber workers.

A number of studies have been conducted in eastern Europe dealing with occupational exposure to butadiene, styrene (or methylstyrene), and other chemicals in synthetic rubber manufacture. While almost all organ systems have been reported to be affected by these compounds, many of the reports are poorly documented, lack adequate controls or fail to provide adequate details about the exposure (Scala, 1977).

Exposure to mixtures of butadiene and styrene resulted in a variety of gastric biliary and hepatic disorders (Bashirov, 1967, 1968, 1970, 1971, 1973; Batkina, 1966; Orlova and Solov'eva, 1962; Volkova et al., 1970).

Occupational exposure to mixtures of predominantly butadiene and styrene or alpha-methyl styrene and other chemicals have resulted in renal dysfunction (Konstantinovaskaya, 1970); endocrine abnormalities (Bashirov, 1973); altered blood indices (Batkina, 1966; Khusainova, 1971); functional disorders of the cardiovascular system (Konstantinovaskaya, 1971); increased blood cholesterol levels (Lukoshina, 1973); dermatitis and alterations in mucous membranes (Volkova et al., 1970); dry palms (Volkova and Bagdinov, 1969); dermatitis (Mirzoyan and Tsai, 1971); unspecified skin diseases (Abdullaeva, 1973); higher incidence of infections, sore throats and illness (Klein et al., 1967); suppressed corneal and peritoneal reflexes, hyperalgesia (Volkova et al., 1970); and nervous system alterations (Gus'kova, 1971; Batkina, 1966). Exposure to mixtures of butadiene, styrene and ethylbenzene have resulted in decreased tonus of the peripheral vascular system (Alekperov et al., 1971); altered electro- and ballisto-cardiograms (Alekperov et al., 1970); hypotension and abnormal myocardial contraction (Vinkurova, 1969); and increases in both capillary permeability and resistance to blood flow (Alekperov et al., 1968).

Numerous respiratory complaints including bronchitis, respiratory irritation, laryngotracheitis and other symptoms and diseases have been reported following occupational exposure to butadiene, styrene and other chemicals (Abdullaeva, 1973; Faustov, 1972; Volkova and Bagdinov, 1969; and Orlova and Solov'eva, 1962).

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

A 24-hour LC_{50} of 71.5 ppm was determined for 1,3-butadiene in a static assay with the pin perch, Lagodon rhomboides (marine species) (Daugherty and Garrett, 1951).

6.2. RESIDUES

Pertinent experimental data regarding 1,3-butadiene residues in aquatic media were not located in the available literature. Veith et al. (1980) have suggested, however, the use of the following equation to estimate bioconcentration factor (BCF) from the octanol-water partition coefficient (K_{ow}):

$$\log BCF = 0.76 \log K_{ow} - 0.23$$

Using this equation and the estimated $\log K_{ow}$ (1.99) from Section 1, the BCF for whole fish is estimated to be ~19.

6.3. CHRONIC EFFECTS, PLANT EFFECTS AND OTHER RELEVANT INFORMATION

Pertinent data regarding the chronic, plant effects and other relevant information of butadiene were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

The American Conference of Governmental Industrial Hygienists (ACGIH, 1981) and The Occupational Safety and Health Administration currently recommend a threshold limit value-time weighted average of 1000 ppm (2200 mg/m³) for butadiene, and ACGIH (1981) also recommends a threshold limit value-short term exposure limit of 1250 ppm (2750 mg/m³).

8. APPROACHES TO RISK ASSESSMENT

Butadiene is a colorless gas at room temperature and is used primarily in the production of rubber and resins. Early reports of the toxic effects of butadiene (Von Oettingen, 1940) have shown that concentrations of 22,130 mg/m^3 result in irritation to the lungs, and cause minor effects, while much higher concentrations (140,000 mg/m^3) result in irritation to the lungs and spleen, and slight hyperplasia of the bone marrow. It was not clear how these findings were confirmed because no other details were given. Miller (1978) reviewed the work of MCA (1974) and Steere (1968) and reported that exposure to butadiene at concentrations below 44,260 mg/m^3 resulted in a mild narcotic effect. Unfortunately, a lower limit of exposure was not stated, and it seems unlikely that at negligible concentrations of butadiene would have a mild narcotic effect. Carpenter et al. (1944) exposed two human volunteers to concentrations of 4425, 8849 and 17,698 mg/m^3 (2000, 4000 and 8000 ppm) butadiene for 8 hours. At the highest concentration, no subjective symptoms were reported.

A number of epidemiologic studies have been reported for the rubber industry, a significant employer of butadiene, and these suggest an excess morbidity and mortality in rubber workers (Miller, 1978). Butadiene, however, has not been implicated in any of these studies, and it should be noted that workers in the rubber industry are exposed to a variety of other chemicals.

Scala (1977) reviewed the eastern European literature concerning occupational exposure to butadiene. Almost every organ system was reported to be affected in some adverse way. Many of the studies, however, were poorly documented and did not include adequate controls, and exposure was not limited to butadiene alone but included styrene and other chemicals. For these reasons, the studies are not particularly useful for risk assessment.

There has been only one study of the chronic toxicity and carcinogenicity of 1,3-butadiene. In this study, performed by Hazleton Laboratories (Owen, 1981), little evidence of systemic toxicity but some evidence of carcinogenicity was found in rats exposed to 1000 ppm (2212 mg/m³) or 8000 ppm (17,701 mg/m³), 6 hours/day, 5 days/week for 105-111 weeks. Statistically significantly increased incidences of both common and uncommon tumor types were associated with exposure to 1000 and 8000 ppm butadiene. Both sexes of treated rats had an increased incidence of Zymbal gland tumors; treated females had increased incidences of mammary tumors, thyroid follicular tumors, and uterine/vaginal stromal tumors; and treated males had increased incidences of Leydig cell tumors and pancreatic exocrine tumors. These results may be adequate as the basis for carcinogenic risk assessment.

Aside from the Hazleton Laboratories study, the available animal data are obtained from subchronic studies (Carpenter et al., 1944; Crouch et al., 1979; Ripp, 1967; Molodyuk, 1969; Nikiforova et al., 1969; Batkina, 1966; Donetskaya and Shvartsapel, 1970; Shvartsapel, 1970) and are not pertinent to an assessment of carcinogenicity. These studies involved inhalation and oral exposure.

Van Duuren et al. (1963) tested a possible metabolite of butadiene, 1,2-epoxybutene-3, for carcinogenicity by skin painting experiments and found only one carcinoma in 30 animals. In a review of this study, as well as another by Van Duuren et al. (1966) the International Agency for Research on Cancer (IARC, 1976), concluded that the data did not allow an evaluation of carcinogenic risk. However, a reevaluation of the more recent animal data by CAG of EPA using IARC criteria suggests a classification of limited. Butadiene has been reported to be mutagenic in the Ames Salmonella assay system in the presence of a liver activation system (DeMeester et al., 1980; Poncelet et al., 1980).

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